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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-763

Approvable Letter (S)

NOT APPROVEABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 50-763

SuperGen, Inc.
Two Annabel Lane, Suite 220
San Ramon, CA 94583

DEC 11 1998

Attention: Sam Boddapati, Ph.D.
Director, Regulatory Affairs

Dear Dr. Boddapati:

Please refer to your new drug application (NDA) dated December 10, 1997, received December 12, 1997, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MITOExtra™ (Mitomycin for Injection).

We acknowledge receipt of your submissions dated February 13, March 13, and November 13 and 20, 1998.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

There is insufficient evidence in the data presented to conclude that MITOExtra™ is bioequivalent to Mutamycin®, as required under 21 CFR 320.33 (b). Using two one-sided t-test procedures for analysis of AUC_t, AUC_{inf}, and C_{max}, bioequivalence of MITOExtra™ and Mutamycin® could not be demonstrated based on comparisons of the 90% confidence intervals for AUC_t (96.6 – 129.4%), AUC_{inf} (97.3 – 130.9%), and C_{max} (91.5 – 134.0%).

FDA does not consider the test of bioequivalence based on the 20/20 rule for the confidence interval an acceptable statistical technique. Utilization of this technique does not fulfill the criteria specified in 21 CFR 320.23 (a) (2).

There was considerable variability in the pharmacokinetic parameters studied. Coefficients of variation (CV) for MITOExtra™ were 65% for AUC_t, 64% for AUC_{inf}, and 86% for C_{max}; whereas, for Mutamycin®, CV were 31%, 32% and 44% for these parameters, respectively. The mean values for AUC_{inf} and C_{max} for MITOExtra™ were about 18% higher than for Mutamycin®. These findings may be explained by the substitution of mannitol with 2-hydroxypropyl-β-cyclodextrin, or by as yet unidentified factors.

We have the following comments and requests for additional information that should be addressed if the application is resubmitted:

General:

1. A re-analysis of study ME001 should be performed using statistical procedures described in the Agency's guidance document entitled, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design". Additional references include Schuirmann, D. J., J Pharmacokin Biopharm 1987: 715:657-680; and Rosner, B., Hypothesis Testing: Two-Sample Inference *in* Fundamentals of Biostatistics, PWS-Kent Publishing Co., Boston, MA, third edition. Patients considered outliers on statistical grounds should be further explored from a physiologic standpoint to provide justification for their exclusion from the re-analysis of this study. Alternatively, a new study demonstrating bioequivalence of MITOExtra™ and Mutamycin® should be performed.

2. The pharmacokinetics of MITOExtra™ should be studied in consecutive cycles of therapy as proposed in study ME2. Considering that MITOExtra™, if approved would be administered for multiple cycles and that circulating derivatives of 2-hydroxypropyl-β-cyclodextrin may influence the distribution and elimination of other co-administered drugs, you are encouraged to obtain blood samples for the pharmacokinetic evaluation of MITOExtra™ in the second and/or third cycles of treatment. Alternatively, a repeat cycle toxicology study in animals to confirm that MITOExtra™ does not pose a worse safety profile relative to Mutamycin® could be performed. This study should incorporate toxicokinetics.

3. A revised package insert should be submitted that describes the results of bioequivalence and other clinical studies performed with MITOExtra™.

4. The Agency's Labeling and Nomenclature Committee will review the proposed name, MITOExtra™, for appropriateness. The use of the suffix "Extra" might convey clinical benefits that are not or cannot be substantiated by data, or may be considered inappropriate.

Pharmacology/Toxicology:

5. Please provide copies of the appropriate references which address data regarding reproductive toxicity, genetic toxicity and carcinogenicity of mitomycin. These findings should be incorporated in the label. The label should conform to the format specified in 21 CFR 201.56 and 201.57. The label of a recently approved drug should be consulted for expected format and content.

6. According to ICH guidelines, individual impurities exceeding 0.1% in the drug substance should be identified. Total impurities in the drug substance were reported to be — %, with individual unidentified impurities reported as not more than —%. Please provide individual impurity specifications of MITOExtra for the batches used in animal studies and intended for marketing so the need for qualification of the impurities can be determined.

7. The NDA indicated that the drug product contained— % total impurities. In addition, —— detected more unidentified impurities in the drug product than the drug

substance. ICH guidelines indicate that the threshold for qualification of degradates in the drug product is —% for a maximum daily dose of 10-100 mg. Please provide individual specifications for the degradates in the drug product.

8. Since systemic exposure to 2-hydroxypropyl-β-cyclodextrin will be significant (9-12 g per cycle considering an adult body surface area of 1.5-2.0 m^2), clinical dosing is proposed for a minimum of two courses, and renal effects were observed preclinically following dosing with 2-hydroxypropyl-β-cyclodextrin and MITOExtra, patients should be monitored for development of renal or bladder toxicities in any further clinical trials.

Chemistry:

9. The primary stability batch and the biobatch were manufactured using bulk mitomycin USP lot # 0973669 supplied by —— Please provide the certificate of analysis for this lot of bulk mitomycin.

10. Upon receipt of the bulk mitomycin USP from —— , tests for identity by —— retention time and an assay of the material are performed as vendor certification as described on p. 246. The method of analysis, with validation data, should be provided.

11. The specifications for 2-hydroxypropyl-β-cyclodextrin, provided in the certificate of analysis on p. 248, should be designated as the NDA regulatory specifications for this material. Additionally, these specifications should be amended to include a specific quantitative test method, with appropriate limits, for 2-hydroxypropyl-β-cyclodextrin as outlined in the USP Pharmaceutical Forum, 21(3), May-June 1995. The possible number of isomers and the number and distribution of the hydroxypropyl groups on the 2-hydroxypropyl-β-cyclodextrin molecule should be investigated for the proposed range of molecular degree of substitution .

12. Please provide complete information, such as certificates of analysis, for the different lots of 2-hydroxypropyl-β-cyclodextrin, identified as —— Lot E8020 and —— Lot 921130, used in the phase solubility studies (Research report #3, p. 819) conducted by —— —— Please include the details of the absorbance method as well as validation data which was used to determine the degrees of substitution and the uncomplexed mitomycin for these samples.

13. The information found in referenced DMF , —— is limited to toxicology data. Consequently, the manufacturing procedures, methods and controls for 2-hydroxypropyl-β-cyclodextrin are not provided in support of the use of the material in the drug product. The applicant (or vendor) should provide a reference to a DMF to access this information, or submit such data to the NDA.

14. Complete information on the 2-hydroxypropyl-β-cyclodextrin reference standard, required by several analytical methods, should be provided. The referenced proposal in the

Pharmaceutical Forum indicates a USP standard for 2-hydroxypropyl-β-cyclodextrin is available.

15. Data supporting a —— year expiration dating period (or retest date) for 2-hydroxypropyl-β-cyclodextrin should be provided. Please note that retesting of a bulk material does not necessarily extend the expiration period of the material for the additional full expiration dating period, but only allows use of the material at the time of the determination of acceptable results. Only full term data can be utilized to set, or extend, the expiration or retest date of any material. The expiration date may be extended on subsequent batches when such test results by the vendor are found acceptable.

16. The source of 2-hydroxypropyl-β-cyclodextrin should be restricted to the manufacturer providing the material used in the bioequivalence studies until the second supplier can be qualified through accumulation of supporting data documenting the equivalency of the material.

17. Given the high levels (2 gm/vial) of 2-hydroxypropyl-β-cyclodextrin in the formulation, please address the effect of viscosity of the solution on the —— of the bulk drug solutions. Does viscosity present any significant problem in filtration time, etc?

18. [redacted]

The formulation overage, therefore, may be justified. Please provide supporting data to justify the overage and address the above noted losses in the levels of mitomycin.

19. Generally, the test for identification of a drug product requires two test methods, one of which is specific. The only identification test for this product is ——— —— . which is not considered specific. Therefore, please provide a second, more specific, identification test in the specifications for the product.

20. The pH range of . —— listed in the specifications for the finished product is considered too wide with regard to drug product quality and for an injectable product. The pH range should be justified, or appropriately tightened based on the manufacturing history of the product.

21. The water content reported on the three lots manufactured to date ranges from — to — %. The proposed specification of not more than — % is considered unacceptable, based on the manufacturing record and the nature of the drug product, i.e., a —— powder. The permitted moisture levels should be reduced to reflect the attainable manufacturing levels, or the current limits justified for this product by supporting stability data.

22. The limits for related substances, i.e., Total Related Substances (NMT —%), Related Substance A (NMT — %), and Related Substance B (NMT —%) are considered

unacceptable as Regulatory Specifications. The limits for each should be tightened to reflect current manufacturing levels. If wider limits are necessary to establish a reasonable expiration period under the stability protocol, a separate set of specifications should be provided for expiration dating purposes.

23. Other Related Substances, identified only by — relative retention times relative to mitomycin on p. 96, were reported by — in bulk mitomycin and MITOExtra. These include:

Mitomycin	MITOExtra

Based on the proposed ICH Guidelines, the structure of any impurity observed at 0.1% or greater should be identified. Please provide information (identity, structure, chemical name, etc.) on all impurities which have been observed above the 0.1% limit, including the Related Substance A and Related Substance B. The information for mitomycin appearing in Analytical Profiles of Drug Substances, 16, pp.361-401 identified — and — as potential degradation products.

24. In the Specifications provided on p. 176, Item E states that the minimum acceptable potency at time of release must be not less than — mg/vial. This corresponds to —% of the label claim. If this is considered an "in-house" specification, please include this limit and test under in-process testing in the manufacture of the product.

25. For a — product, the specifications should be revised to include the reconstitution time, indicating the diluent preferences with justification.

26. As with all injectable products, an examination for particulates upon reconstitution should be included, at appropriate intervals, under the stability protocol.

27. The manufacturer of drug product lot #0253268, as the bio-batch, should be specified. The high reported assay of — % of label claim, although within specifications, should be addressed, since it exceeds the proposed overage of—%.

28. The drug product lot #0253268 is out of specification for Related Substance B at the 17 and 24 month testing period. Therefore, an expiration dating period of—months is not permitted at this time. Upon the accumulation of sufficient data on three lots of drug product, a statistical analysis of the stability data should be performed to support the

proposed expiration dating period, as described in the FDA Guidance. This is in lieu of full term data.

29. With regard to the stability of the reconstituted solution of drug product lot #0253268 on page 170 & following, the data should include tests and specifications for degradation products, such as Related Substance B, and any others. You may also consider including a test for 2-hydroxypropyl-β-cyclodextrin under the protocol until sufficient data are available to indicate no degradation is occurring for this component.

30. No information is provided on the levels of extractables which might leach from the IV administration sets as a result of the formulation containing 2-hydroxyproply-β-cyclodextrin. A study should be initiated to determine if extractables are a significant problem.

31. The admixed solution, containing 5 mg (20.0 ug/mL nominal) MITOExtra in D5W, drops below the lower specification limit at 3 hours (— ; and measures — at 4 hours. However, the solution containing 10 mg (40 ug/mL nominal) remains within the lower limit at the 4 hour reporting period. Based on the reported data at three and fours hours, further studies to determine the effect of concentration are indicated. Other parameters, such as pH, should also be measured and studies initiated to determine if pH, for example, has an influence on the stability of the active pharmaceutical ingredient in the admixed solution.

32. The stability data for MITOExtra at nominal concentrations of 20 ug/mL and 40 ug/ml in approximately 240 mL of 0.9% sodium lactate admixed in plastic IV bags, support a use of 24 hours based on assay results of —— %, respectively. At 48 hours, the assay values were — % for both concentrations. The intravenous summary table and labeling for the sodium lactate admixed solution should be amended to indicate that the admixed solution is stable only for 24 hours, by stating, "use within 24 hours after preparation" in the labeling.

Microbiological:

33. Describe in more detail the overall manufacturing operation of the specific drug product in this NDA. Please include the normal flow of product, components to finished drug product, identify specific equipment, manufacturing rooms and fill lines. Specify the type of container and closure systems used for this drug product.

34. Describe the drug product filtration process. Indicate the type and configuration of filters used. Provide product specific filter validation data that demonstrates that the filters are capable of retaining microorganisms.

35. Describe any bulk solution holding periods and indicate how the microbial quality of the bulk is maintained during the holding periods. Submit information and specifications regarding the total bioburden load of the prefiltration bulk drug product.

36. Submit sterilization — summary validation data and information for the containers, closures, equipment and related components that contact the drug product. For items sterilized in — describe the type of — the performance specifications and monitoring procedures for routine production cycles. The cycle specifications should include minimum and maximum F_0 in addition to temperature, pressure and cycle parameters. Submit sterilization validation information and data for components sterilized in the — in accordance with the 1994 FDA Guidance on Sterilization Validation. This information should include descriptions of — during validation runs. Validation runs should include heat distribution and heat penetration studies under worse case (suboptimal) conditions. The commercial source and the performance characteristics of the biological indicators used should be described.

For items sterilized — in the — , describe the routine production cycle, monitoring procedures and performance specifications. Submit sterilization validation information and summary data that includes heat distribution and penetration summaries, biological challenge studies with endotoxin.

Identify the — used to manufacture the drug product and submit summary sterilization validation information and data. Indicate whether — is used for — chambers during media fill simulations and during production.

37. With regard to the microbiological monitoring program, the number and location of sites monitored during media fills and production runs should be indicated. Diagram of sites monitored is helpful. Please clarify what — stands for in the Table on page 680 of Section 3.3.

38. With respect to action taken in the event of failed media fills, it is not clear what is meant by "the disposition will be documented" (p. 681, Section 3.3). Product manufactured by a non-validated process should not be marketed.

39. The ability of the container/closure system to maintain the sterility of the drug product should be demonstrated. Submit information and data that shows that the container/closure system is capable of maintaining microbial integrity.

40. Submit release specifications for the drug product and include Sterility and Bacterial Endotoxin release criteria and specifications. Submit the sterility protocol and summary validation data. State if the protocol for sterility is in accordance with the USP<71> method. Summarize the validation protocol and summary data of the Bacterial Endotoxin test used to assess endotoxin in the drug product. Provide data from the three validation (qualification) lots.

41. Describe the stability protocol for this drug product and indicate whether the stability protocol includes a sterility test initially and at expiry. Consider conducting container-closure integrity studies to show that the microbial integrity of the container-closure can be maintained over the shelf-life of the product in lieu of sterility tests on stability samples at expiry.

42. Submit data and information to show that the drug product reconstituted as described on the label does not support microbial growth during storage. A modified USP <51> Antimicrobial Preservative Effectiveness Test (APET) conducted with the reconstituted drug product to evaluate the growth of low inoculum levels (—) of microorganisms described in the USP APET procedure during the intended storage period and temperatures may be appropriate for this purpose.

43. Refer to the FDA "Guideline for Submitting Documentation for Sterilization Process Validation in Application for Human and Veterinary Drug Products" issued in November 1994 for the type of information that should be submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Debra Catterson, Project Manager, at (301) 827-1544.

Sincerely,

/S/ M.D. 12/11/98

Robert Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 50-763
HFD-150/Div. Files
HFD-002/ORM
HFD-101/Office Director
HFD-95/DDMS
HFD-810/DNDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-805/PFHughes
HFD-150/DGriebel
HFD-150/JBeitz
HFD-150/RJustice
HFD-150/RBarron
HFD-150/RWood
HFD-150/MBrower
HFD-150/PAndrews
HFD-150/EMishina
HFD-150/ARahman
HFD-150/DPease
HFD-150/LVaccari
HFD-150/DCatterson

Drafted by: DCatterson/12.3.98

Initialed by: DPease/12.4.98
JBeitz/12.7.98
RBarron/12.7.98
RWood/12.9.98
MBrower/12.4.98
PAndrews/12.4.98
EMishina/12.4.98
ARahman/12.4.98
RJustice/12.9.98

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RBarron/12.11.98
RJustice/ 12.11.98
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NOT APPROVABLE (NA)